Remarks

This Amendment is being submitted in response to the Office Action mailed January 23, 2007 in connection with the above-identified application. Applicants are concurrently submitting a Petition to Revive under 37 C.F.R. § 1.137, along with all of the documents and information required for the petition.

Amendments

Claim 1 is amended to more particularly point out that the antigenic protein molecule (i) is an TNFα protein, and the carrier protein molecule (ii) is a KLH protein molecule. Amended claim 1 further specifies that more than 1% (and less than 40%) of the TNFα proteins are covalently bound to the KLH carrier protein molecules. Finally, amended claim 1 now further recites that covalent bonds between one or more TNFα proteins and the KLH protein molecule are made through a bifunctional bond chemical agent consisting of glutaraldehyde. These amendments are supported generally in the specification (*see, e.g.* p. 22, line 5, p. 15, line 20, and the original claims, such as original claims 8, 10, and 20.)

Corresponding changes have been made to claims 2, 3, and 5. Claims 4, 6-10, and 29 have been cancelled. Claims 11-20 and 26-28 have been withdrawn from consideration. With this amendment, claims 1-3, 5, and 21-28 are pending.

No new matter has been added, and entry of the amendments is respectfully requested.

In addition, applicants have submitted a substitute specification, pursuant to the requirements of 37 CFR 1.125 in order to address the Examiner's objections to the specification. Applicants enclose as Exhibit B a substitute specification with markings showing all the changes relative to the immediate prior version of the specification of record. An clean version (without markings) is enclosed as Exhibit A. No new matter has been added.

The claims are now directed to a stable immunogenic product for inducing antibodies raised against a TNFα protein. The stable immunogenic product comprises heterocomplexes between TNFα protein molecules and KLH (keyhole limpet haemagglutinin), where more than 1% and less than 40% of the TNFα proteins are covalently linked to the KLH carrier protein molecules. The claims also specify that the covalent bonds between one or more TNFα proteins and the KLH protein molecule are made through a bifunctional bond chemical agent consisting of glutaraldehyde.

Provisional Double Patenting Rejection

The Examiner has provisionally rejected claims 1-10, 21-25, and 29 on the grounds of non-statutory obviousness-type double patenting over claims 26 and 27 of copending Application Serial No. 11/135,660. Applicants do not necessarily agree with the Examiner's analysis, but will defer responding to it until the rejection is no longer provisional.

Written Description and Enablement Rejections Under § 112

The Examiner has rejected claims 1-10, 21-25, and 29 under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the enablement requirement. The Examiner has also rejected claims 1-10, 21-25, and 29 under 35 U.S.C. § 112, first paragraph for allegedly failing to comply with the written description requirement. Applicants strongly traverse both rejections.

Turning first to the enablement rejection, the Examiner appears to have recognized that the specification is replete with guidance for preparing heterocomplexes comprising TNFα as the antigenic proteins and KLH as the carrier (*see*, Office Action, p. 6). Furthermore, the coupling of an antigenic protein with a carrier protein such as KLH is fully disclosed and enabled in the specification (see,

examples 1-10). The specific preparation of a stable immunogenic product comprising heterocomplexes of TNFα and KLH is the subject matter of example 9.

With respect to the alleged lack of guidance in the specification as to how "to produce and/or maintain" more than 1% and less than 40% of covalent bonds between TNFα protein molecules and KLH carrier protein molecules, example 9 shows a fully disclosed embodiment of a method for preparing a stable immunogenic product as defined by the claims.[1] The specification fully discloses methods for determining the percentage of antigenic molecules of interest (i.e. TNFα) covalently linked to the carrier protein molecules (i.e. KLH) (see, page 9, line 4 – page 12, line 14; see also page 39, line 25 – page 41, line 31. From the foregoing, it is apparent that the specification fully enables one of ordinary skill in the art to practice the claimed invention, by simply adapting the amount of glutaraldehyde used and the reaction time period to obtain the specified percentage range of covalent links.

With regards to the alleged lack of written description and enablement for preparing stable immunogenic product starting from TNFα other than the murine TNFα which is disclosed in the examples, applicants respectfully traverse.

Applicants have attached as Exhibit C a table which depicts the amino acid identity scores resulting from the comparison of the amino acid sequence of human TNFα and various amino acid sequences from TNFα from other species. The identity of each TNFα amino acid sequence which is compared is defined by a reference to its corresponding accession number in the SwissProt database. The identity score was determined using the conventional sequence comparison program Clustalw with the default parameters.

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[1] The Examiner has also alleged that "the specification...fails to provide enabling support for any vaccine composition" (Office Action, p. 6). Presumably, this rejection would apply only to claim 24 (the only claim which recites "a vaccine composition.") In any event, contrary to the Examiner's contention, one of ordinary skill in the art would be able to produce and use the composition of claim 24.

The table shows that TNFα is a highly conserved protein amongst species with more than 95% amino acid identity among primates, and more than about 80% identity among mammals. However, the table also shows that human TNFα and murine TNFα are among the less similar TNFα sequences. Nevertheless, even this amount of difference between the amino acid sequences of human TNFα and murine TNFα does not induce significant structural change in the three dimensional conformation of the protein.

Exhibit D shows three dimensional structural comparison between human TNFα and TNFα originating from macaque (A), pig (B), dog (C), and mouse (D).[2] It may be seen that all structure pairs which are compared are almost superimpositions of one over the other. The binding domains to TNFα with the $TNFR_1$ and $TNFR_2$ receptors appear in grey. Regarding Figure D in particular – comparing human and murine TNFα with a relatively low (79.8%) identity score – it should be noted that these two structures are quasi-superimposed on each other. Typically, the 3D structure of TNFα from human and mouse as shown a Z-score of 6.7, which confirms that the alignments are true ones, and not due to chance.

From the foregoing remarks and figures, it is apparent that the amino acid sequences of TNFα originating from various species are highly conserved and the resulting 3-D structures are practically identical, including the TNFα binding domains to its receptors. As such, the specification's admitted disclosure of the claimed stable immunogenic product with murine TNFα is fully enabling for stable immunogenic products containing a TNFα protein, regardless of the species from which it is derived.[3]

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[2] In order to generate figures A-D, the 3-D structures of the TNFα molecules that are compared were aligned using a bio informatics tool termed "the combinatorial extension method" disclosed, for example, at http://cl.sdsc.edu/ce.html. The alignment visualization was performed using the bio informatics tool called RasMol which is available at www.bernstein-plus-sons.com/software/RasMolunderscore2.7.1/. For the comparison between murine and human TNFα, the TNFα 3-D structures were retrieved from the P-DBsum website www.biochem.ucl.ac.uk/bsm/pdbsum/.

[3] From a written description perspective, it is also worth noting that "TNFα" as a generic protein is quite clearly described in the specification and the original claims (See, eg. p. 22, line 5, and original claim 10).

Indefiniteness Rejections Under § 112

The Examiner has rejected claims 1-10, 21-25, and 29 under 35 U.S.C. § 112 as on the grounds than the phrase "less than 40% of the antigenic proteins" allegedly renders the claim indefinite because there is no lower limit. As noted above, the claims now recites that more than 1% of the TNFα must be covalently linked to the KLH carrier molecules, obviating this rejection.

Claim 25 was also rejected as being indefinite on the grounds that the phrase "CpG immunity adjuvant" is allegedly indefinite. Applicants traverse. The use of a CpG immunity adjuvant for raising an immune response in humans was fully part of the general technical knowledge of one of ordinary skill in the art at the time the invention was made. To demonstrate this applicants enclose as Exhibit E, copies of 11 abstracts of scientific articles – published in the three years preceding the priority date of the present application - relating to the use of CpG adjuvants to trigger an immune response in humans.

The foregoing shows that the term "CpG immunity adjuvant" is well understood by persons of ordinary skill in the art. Therefore, this rejection should be reconsidered and withdrawn.

Rejections Under § 102

Wedlock

The Examiner has rejected claims 1-4, 9-10, 21-24, and 29 under 35 U.S.C. § 102(b) as allegedly being anticipated by Wedlock et al., (Immunol. And Cell Biology, 1999, 77:28-33) ("Wedlock"). The Examiner's rejection claims that "[Wedlock] teach an immunogenic composition comprising KLH and brushtail possum-TNFα in a PBS buffer." (Office Action, p. 13). Applicants respectfully traverse this rejection.

Wedlock is an academic study aimed at determining the adjuvant effect of TNFα for inducing an antibody response to KLH in possums (for use in providing birth control to possums). Thus, in Wedlock, the possum's TNFα protein is not used as an antigenic protein. Instead, in Wedlock TNFα is being assayed for its potential biological activity of a cytokine adjuvant of the immune response. Furthermore, Wedlock discloses, at most, a buffer solution comprising (i) free KLH proteins and (ii) free TNFα proteins (from possums). In the buffer solution disclosed by Wedlock, the TNFα and KLH molecules are not linked together, much less covalently linked.

In addition, the Examiner has failed to show how Wedlock discloses each and every limitation of the claims. Without such a showing, the rejection must be withdrawn.

In light of the foregoing, applicants respectfully request reconsideration and withdrawal of the rejection over Wedlock.

Zagury

The Examiner has also rejected claims 1-4, 6-10, 21-25, and 29 under 35 U.S.C. § 102(b) as allegedly being anticipated by Zagury, et al., WO 02/011759 A1 ('Zagury"). According to the Examiner:

> "Zagury et al., teach immunogenic compositions with an anti-cytokine effect comprising an immunogen, including TNFα conjugated to a carrier protein, including KLH...The immunogenic complex of KLH and TNFα is taught using glutaraldehyde at p. 22..."

(Office Action, p. 14). Applicants traverse this rejection.

TNFα is cited in Zagury. However, Zagury does not disclose <u>any</u> protein conjugate between TNFα and KLH. Zagury does disclose other antigenic protein-KLH conjugates. Moreover, Zagury only discloses conjugates wherein the antigenic protein is <u>exclusively</u> linked to the carrier protein by covalent bonding (100%). Thus, Zagury does not anticipate the claimed invention.

Zagury relates to vaccine compositions comprising modified cytokines and growth factors. In some embodiments disclosed in Zagury, the modified antigens are conjugated to a carrier protein – KLH. However, in these conjugated products, the antigenic protein is linked to the carrier protein exclusively through covalent bonds. This is in accordance with the conventional conjugation techniques between an antigen and a carrier protein which were largely disclosed in the literature and which were well known to those of skill in the art. Specifically, the conjugation technique used in Zagury involves a step for removing excess products (antigens) which have not reacted with the coupling reagent, which results in 100% covalent linkages. In Zagury, removal of excess products not coupled through covalent bonds is performed by size exclusion chromatograph (see, e.g. ¶ 158 of US 2004/0028647, the English language counterpart of Zagury).

The conjugated products disclosed in Zagury are purely conventional, such as those disclosed at page 2 of the present specification. A copy of one such reference, Richard et al. (2000) is attached as Exhibit F for the Examiner's convenience. Richard uses a preparation similar to that disclosed in Zagury, comprising a step for removing the excess products not covalently linked after the conjugation step. This step consists of removing the non-reacted products by size exclusion chromatography (see p. 767 of Richard, last paragraph in the right hand column).

In summary, Zagury disclosed conjugated products wherein the antigenic protein of interest and the carrier protein are linked exclusively through covalent bonds. Therefore, even disregarding the lack of disclosure of a TNFα-KLH conjugate, Zagury cannot anticipate the pending claims, which recite that less than 40% of the TNFα proteins are covalently linked to the KLH carrier protein.

Conclusion

Applicant respectfully submits that the claims are in condition for allowance, and earnestly solicits prompt notice to that effect. If the Examiner believes that a personal interview or telephone call could advance prosecution of this application, please contact the undersigned.

Respectfully submitted,

JACOBSON HOLMAN PLLC

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By: _____
N. Whitney Wilson
Registration No. 38,661

Customer No. 00,136
400 Seventh Street, N.W.
Washington, D.C. 20004
(202) 638-6666